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Surgical Management of Complications of Steroid Therapy

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GLUCOCORTICOIDS, introduced in 1949, are steroids with anti-inflammatory and gluconeogenic effects. In certain disease states these agents are life-sustaining and in others they provide significant therapeutic benefit. Their use, however, may be associated with serious and at times fatal complications. This report reviews the current status of the surgical management of these complications which involve the gastrointestinal tract, pancreas, infection and host defense mechanisms, visual acuity, wound healing and the skeletal system. Extensive general reviews have been conducted on the clinical and metabolic consequences of the use of adrenal glucocorticoids,[5,36,131–133] and no attempt will be made to duplicate these efforts. Considerations involving the use of steroid therapy include the seriousness of the underlying illness, the duration of therapy and the expected results of treatment versus the risks of encountering the known hazards of the drug. These factors all contribute to the justification of the clinical use of adrenal glucocorticoids and at the same time necessitate thoughtful consideration regarding their therapeutic indication.

Clinical Pharmacology and Physiology

The biologic effects of glucocorticoids relate primarily to carbohydrate metabolism, promotion of gluconeogenesis, deposition of liver glycogen and increased blood glucose concentrations. Cortisol and its synthetic analogs have significant glucocorticoid activity with the relative potency listed in Table 1. Depending upon their ability to affect carbohydrate metabolism all have biologic properties with special clinical significance.[55] These properties include: 1) *Protein wasting activity*. The breakdown of proteins is accelerated by glucocorticoids which inhibit amino acid uptake and protein synthesis by extrahepatic tissue. The chronic presence of increased plasma and tissue concentration of glucocorticoids suppresses growth hormone secretion with inhibition of body growth. 2) *ACTH suppressing activity*. Suppression of the synthesis and secretion of ACTH occurs with excess administration of glucocorticoids. 3) *Anti-inflammatory activity*. Excessive amounts of glucocorticoids inhibit or suppress the allergic and inflammatory response to tissue injury. The mechanisms for these effects are not entirely understood but include lysosomal stabilization with inhibition of leukocyte diapedesis across capillary endothelium and migration through tissue. In addition, they interfere with the host response to bacterial infection. 4) *Additional effects* of glucocorticoids include lympholysis, decrease in antibody production, stimulation of hematopoesis, increased fat deposition in the face, neck and trunk, reduction in muscular strength, promotion of uric acid and free water excretion, and increased appetite. Although the mineralocorticoid effects of cortisol and corticosterone are less than those associated with aldosterone, there are still significant side effects related to potassium depletion, excessive sodium retention, edema and hypertension.

Hypercortisolism (Cushing's Syndrome) in the context of this discussion will be limited to the syndrome created by the exogenous administration of glucocorticoid drugs. This form of iatrogenic Cushing's Syndrome, commonly seen in patients receiving long-term corticosteroid therapy, is rarely noted when brief elevations of cortisol are used for therapeutic purposes. The clinical characteristics include easy bruising, thin skin with visible veins and pink or purple straiae,

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TABLE 1. *Classification of Glucocorticoids*

Oral Preparation and Available Doses (mg)	Equivalent Potency (mg)	Plasma Half-life (min)	Anti-inflammatory Potency (mg)	Sodium Retaining Potency (mg)	Pituitary Suppressive Activity	Suitable for Alternate-day Therapy
Short-acting						
Hydrocortisone						
5,10,20	20	30	1	1	+	No
Cortisone						
5,10,25	25	110	0.8	1	+	No
Prednisone						
1,2.5,5,10,20,50	5	60	3.5	0.5	+	Yes
Prednisolone						
1,2.5,5	5	200	4	0.5	+	Yes
Methylprednisolone						
2,4,16	4	180	5	0.25	+	Yes
Intermediate-acting						
Triamcinolone						
1,2,4,8,16	4	300	5	0.1	++	No
Paramethasone acetate						
1,2	2		10	0.1	++	No
Long-acting						
Betamethasone						
0.5	0.60		25	0.05	+++	No
Dexamethasone						
0.25,0.5,0.75,1.5	0.75	200	30	0.05	+++	No

Source: Frawley, T. F.: Postgrad. Med., 56: 4:123, 1974.

muscle weakness most often noted in the quadricep muscles and wasting of the extremities. Generalized osteoporosis may occur and frequently involves the vertebral column resulting in compression fractures. Hypercalciuria is common with urinary calcium levels reaching 150 to 300 mg per day. Growth in children may be diminished and often ceases if the epiphyses close. It has been estimated that approximately 90% of patients with Cushing's Syndrome will demonstrate mild impairment of glucose tolerance characterized by elevated blood glucose levels two and three hours following ingestion of oral glucose. Hypertension, edema and hypokalemia, frequently observed in patients receiving large amounts of exogenous steroids, will gradually subside as the dosage is reduced. Additional features include an increase in color of the faciocervical region, oligomenorrhea and hirsuitism. Emotional lability has been reported and is occasionally associated with depression. Approximately one-third of patients with Cushing's Syndrome have tinea versicolor. These signs and symptoms are more frequently noted with exogenous steroid administration on a two or three time daily basis and considerably less common when the drugs are given once a day in the morning or on an alternate day basis.

An additional factor contributing to the inconstant and unpredictable individual response to these agents relates to the metabolic clearance rate and serum half life of prednisone. There is considerable variability regarding the degradation of exogenous corticosteroids and the slower the metabolic clearance rate the more severe the side effects of Cushing's Syndrome.[77] This observation could explain the different response portrayed by patients to the same dosage of steroids. It is of interest that the therapeutic benefits of corticosteroids are not related to the metabolic clearance rate of prednisone, and the clinical response to treatment can not be correlated with the severity of Cushing's Syndrome.[77]

The response of the Hypothalamic-Pituitary-Adrenal gland (HPA) axis to stress during surgery has been studied by measuring the increase in plasma levels of ACTH,[40,97] 17 hydroxycorticosteroids (17-OHCS) or 11 hydroxycorticosteroids (11-OHCS),[65,126] and in urinary 17 hydroxycorticosteroids (17-OHCS).[92,97,126] The rise in plasma 17-OHCS during operation in patients with an intact spinal cord is secondary to a rise in plasma ACTH.[69] Paraplegic patients, however, do not exhibit the same response during operation and fail to excrete the same amounts of 17-OHCS from the adrenal vein unless stimulated by exogenous ACTH.[69] "Adrenal exhaustion" has been referred to as a potentially life threatening complication of patients treated with adrenal glucocorticoid therapy and subjected to stress. However, well documented case reports are rare if substitution therapy was administered in the proper amount. Moore *et al.*[92] commented that in their experience "adrenal exhaustion" was rarely encountered outside of frank endocrine disease, adrenal removal or cortisone withdrawal.

The effect of long-term corticosteroid therapy upon the HPA axis has been studied in patients by measuring

plasma cortisol[83] and the response to a standard insulin-induced hypoglycemia.[81,83] Recovery of adrenal function after long-term corticosteroid therapy is related to the duration of treatment and the dosage administered.[81] It is of some interest that plasma cortisol levels returned to normal more quickly than the response to insulin-induced hypoglycemia. The use of an alternate day prednisone schedule diminishes the undesirable side effects of glucocorticoids but will still significantly impair function of the HPA axis.[83] It is important to recognize that the use of alternate day prednisone still places the patient at risk to the potential effects of hypoadrenalism; and therefore, an increase in corticosteroid dosage should be employed if the individual is placed in a position of stress.

The need for additional corticosteroid coverage during surgical stress has been studied,[71] and although hypotension is rarely reported during surgical stress in patients receiving relatively small amounts of prednisone (6.5 mg/day), supplementary steroid support is advisable. It is probable that daily prednisone levels of 20 mg/day or greater do not require additional steroid coverage. The amount and duration of steroid coverage are largely empirical as is the rate of reduction to the pretreatment level.

The weaning of patients from long-term corticosteroid therapy must be done gradually to avoid hypoadrenalism. Although the revival of adrenal function can be monitored by measuring the plasma levels of 11-OHCS or cortisol, most physicians manage steroid withdrawal by cautious clinical observation, and in spite of long-term treatment complete adrenal responsiveness can almost always be restored.[31] The pituitary adrenal axis can remain subnormal for several months after cessation of glucocorticoid therapy (See Fig. 1), and external stress by either surgery or illness may even further reduce the adrenal response. The latter consideration has been generally determined by clinical observation, and objective data to confirm this suspicion is not available.[31] The use of corticotrophin to assist in adrenal revival is now seldom used.

Rapid or abrupt withdrawal of corticosteroids has been reported to be associated with the syndrome called "pseudorheumatism."[114] This syndrome is characterized by restlessness, anorexia, nausea, lethargy, memory deficit, emotional lability, arthralgia, osseous and muscular pain, paresthesias and diminished sensation to pin prick. Although these events may be seen in patients receiving steroids for reasons other than rheumatoid disease, it is most probably the result of a significant and sudden change in dosage, and not related to hypoadrenocorticism or hypoadrenocorticotropism.[3] The treatment is symptomatic consisting of mild analgesics until the symptoms subside or an increase in the steroid dosage to the previous level followed by slow withdrawal. In most instances the duration is limited to 7 to 10 days and subsides spontaneously.

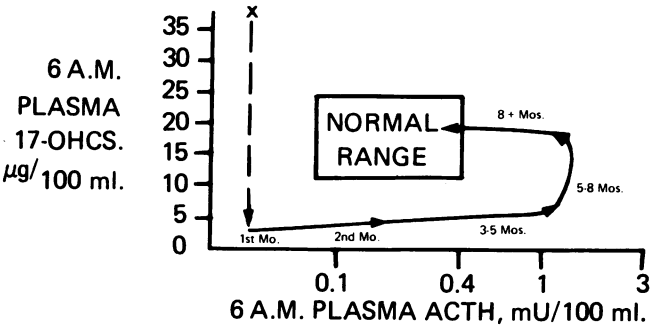

FIG. 1. Relationship between plasma ACTH and plasma 17-OHCS (cortisol) concentration during recovery from severe, prolonged pituitary-adrenal suppression with exogenous corticosteroids or autonomously secreted cortisol. From: G. W. Liddle and K. L. Melmon: The Adrenals, *In*: Textbook of Endocrinology, (Ch. 5) Edited by Robert H. Williams, 5th ed., Philadelphia, W. B. Saunders Company.

Gastrointestinal

The complications best known to the general surgeon and least well documented by statistical analysis relate to the effects of corticosteroids upon the gastrointestinal tract. Since the advent of glucocorticoid therapy for rheumatoid disease, serious and often life threatening complications associated with perforation or bleeding of the esophagus, stomach, small and large intestine have been reported. The crucial and as yet unanswered question is whether or not there is a cause and effect relationship of these complications with steroid administration. Several extensive reviews[16,28,34,87] of patients receiving steroids for various diseases have not supported the earlier impression that these pharmacologic agents cause bleeding or perforation of the gastrointestinal tract. However, because of the general impression that many of these complications were "steroid-induced," the pertinent English literature was reviewed.

The complications most often reported are those of mucosal ulceration with bleeding or perforation, and both have a high morbidity and mortality depending upon the age, primary disease and general condition of the patient prior to perforation. As a rule the more distal the site of perforation in the intestinal tract, the more difficult it is to establish a correct diagnosis when patients are receiving steroid therapy. Consequently, the mortality rates are highest with involvement of the large bowel. The clinical symptoms of perforation are less marked in patients receiving corticosteroid therapy. Abdominal pain may be minimal with few symptoms relating to the gastrointestinal

system. Abdominal distension and hypoactive bowel sounds are often associated with a mild degree of tenderness and guarding to palpation. Leukocytosis is frequently absent, and the most reliable radiologic finding is the presence of free intraperitoneal air. Gastrointestinal bleeding is usually secondary to gastroduodenal ulceration although bleeding from colonic ulceration has been reported.[129] Diagnostic studies, essential for proper management, include endoscopy, selective arteriography, and barium contrast studies of the stomach, small and large intestine. The usual criteria for surgical intervention in patients with gastrointestinal bleeding are applicable in patients receiving corticosteroids.

Esophagus. Ulcerations of the esophagus in patients receiving corticosteroid therapy[2,116] are infrequent in comparison to the occurrence of these lesions in the stomach, small and large intestine. Rarely they cause bleeding or perforation.[54] Dysphagia, often improved with symptomatic therapy, is a common complaint. Esophageal ulcerations in recipients of renal allografts most often occur after one or more episodes of rejection requiring high dose steroid therapy for reversal of rejection. In this group of patients, the ulcers may be secondarily infected with candida. The duration of symptoms in the post transplant patient is usually between 7 and 20 days with the natural history one of gradual improvement. On occasion cytomegalovirus inclusion bodies have been noted at the base of the ulcer, but it is not known whether the virus itself causes the ulcer or is attracted to the area because of the inflammatory response surrounding the lesion.

Gastroduodenal. Gastroduodenal ulceration "steroid ulcer" is a serious complication estimated to occur in 10 to 30% of patients requiring steroid treatment for more than one month.[73] The pathogenesis of gastroduodenal peptic ulceration in patients receiving glucocorticoid therapy is unclear.[29,87] Adrenalectomy decreases acid secretion in the canine.[30] Glucocorticoids given for brief periods in the dog have no effect on acid secretion, whereas chronic corticosteroid administration increases acid and pepsin secretion. Comparable data in man are unavailable. An immediate and direct ulcerogenic effect of glucocorticoids upon the gastric mucosa has not yet been demonstrated in the experimental animal.[122] The reduction of epithelial cell renewal in the gastric mucosa and the decrease in the secretion rate of mucous in the stomach of the dog[88] suggest that mucosal injury may be a factor in the production of gastroduodenal ulceration. These experimental data, however, have yet to find a place in the explanation of the suggested increase in peptic ulceration in patients receiving corticosteroid therapy.

The association of cytomegalovirus to massive upper gastrointestinal bleeding has been reported in a renal allograft recipient receiving steroids,[37] and a similar involvement of gastric ulceration with this virus has been recognized by others.[89,113] However, it is difficult to establish a cause and effect relationship between corticosteroid therapy, cytomegalovirus and mucosal ulceration.

Patients receiving steroids for rheumatoid arthritis have been reported to have a greater incidence of gastroduodenal ulceration[73] than those individuals receiving similar treatment for ulcerative colitis,[136] suggesting that the underlying disease itself or other additional drugs may play a role in the pathogenesis of ulcer formation. Kammerer and coworkers[73] studied routine barium contrast examinations of the stomach in an uncontrolled series of patients receiving steroids for rheumatoid arthritis and found radiographic evidence of peptic ulceration in 31%. Another prospective but uncontrolled study reported a high incidence of gastric and duodenal ulceration in 19% of patients with rheumatoid arthritis treated with corticosteroids.[53] Other investigators have failed to find an increased incidence of peptic ulcer disease in patients with rheumatoid arthritis treated with steroids.[16,28,87]

The above etiologic and therapeutic considerations are less conclusive in view of a recent review of 5331 patients receiving adrenocorticosteroid therapy for a variety of medical illnesses. This analysis failed to support the earlier conclusions that a strong correlation existed between steroid therapy and gastroduodenal ulceration.[28] Therefore, because of this study the earlier reports of peptic ulceration in conjunction with the use of adrenocorticosteroids must continue to be carefully reevaluated.

The relationship of steroid dosage to ulceration has been reported to exist when the amount of cortisone administered exceeds 50 mg per day or prednisone is given in the dosage range of 20 mg per day. However, more than 20 mg per day of prednisone does not seem to be associated with a progressive increase in ulceration.[75,129] To date there is no evidence that one form of corticosteroid medication is more or less "ulcerogenic" than another.

"Steroid-induced" ulcer of the stomach and duodenum may cause mild indigestion or present initially with massive upper gastrointestinal hemorrhage or perforation. Pain is less severe in patients with peptic ulceration coexistent with steroid therapy possibly because of the anti-inflammatory effects of corticosteroids. The silent nature of the "steroid ulcer" has been confirmed with routine upper gastrointestinal x-ray studies revealing approximately one-third of all patients receiving corticosteroids to have ulcers of the stomach and duodenum.[73] Ulcers associated with corticosteroid therapy are frequently located in the gastric antrum and on the lesser curvature.[73,124] To

palpation they are usually soft and pliable with a minimal inflammatory reaction by gross and microscopic examination. Others have noted gastric ulcers to be large, deep and penetrating with little relationship to hyperacidity.[73]

The prophylactic use of antacids has been reported to be beneficial in preventing ulcer formation during steroid therapy and concomitant usage of acetylsalicylic acid generally contraindicated[124]; however, a randomized prospective clinical study examining this question has not yet been reported. Patients developing gastroduodenal ulceration during adrenal steroid treatment should be managed by intensive medical therapy since either bleeding and or perforation are serious complications associated with both a high morbidity and mortality.[54,112] If endoscopic, cytologic and radiologic studies favor a benign ulcer, then prolonged medical management of 6 to 8 weeks may be necessary to accomplish complete healing. Patients with persistent ulceration in spite of appropriate medical treatment should be considered for surgical treatment although the natural history of this type of ulcer has not been well studied. There are no available data concerning the incidence of malignancy in gastric ulceration associated with steroid therapy.

The operative procedure providing the best results for patients with peptic ulcer disease receiving corticosteroid therapy has yet to be determined. Antrectomy and vagotomy or pyloroplasty and vagotomy would seem to be the procedures of choice depending upon the location of the ulcer and the age and condition of the patient.

Small intestine. Ulceration of the small intestine has been reported to occur after prolonged corticosteroid therapy[54,61,84] and is more commonly located in the jejunum. These ulcers often present with bleeding or perforation and have little prior symptomatology. Perforation is not infrequent and has been reported to have a high mortality.[54] Although there are a considerable number of isolated case reports regarding this clinical entity, statistical evidence for a cause and effect relationship to corticosteroid therapy is lacking.[34]

Colon. Complications of long-term corticosteroid therapy involving the colon have been reported with less frequency than those noted with the upper gastrointestinal tract. However, the morbidity and mortality are significant when associated with either bleeding or perforation. Colonic perforation may result from diverticular disease or on occasion occurs spontaneously. The perforation may be free into the peritoneal cavity causing generalized fecal peritonitis or may penetrate into the mesentery resulting in abscess formation. Patients receiving corticosteroid therapy seem to be particularly at risk for colonic perforation and have a high mortality rate.[44,62,102,108,116,127,140] Symptoms usually minimal before perforation are frequently unimpressive even after perforation and peritonitis have occurred. Failure to promptly establish the correct diagnosis has delayed surgical intervention and has contributed to the poor results reported. This complication occurs more often in patients over the age of 45, coincident with the increased frequency of diverticulosis. Free perforation is not unusual in patients receiving corticosteroid therapy; however, complications resulting from fistulae formation seem to be less frequent.[24] The reported high mortality and morbidity in patients with perforated diverticular disease of the colon increases when the patient has received steroid therapy.

Surgical management of colonic bleeding or perforation depends upon the etiology and location of the disease process. Involvement of the right colon with either of these two entities may be managed by resection and ileotransverse colostomy with a primary anastomosis if peritoneal contamination is minimal and the general condition of the patient acceptable.[85] In the presence of generalized peritonitis and or intra-abdominal abscess formation an ileostomy and mucous fistula might be more expeditious and avoid the possibility of anastomotic leakage. The same pathologic process on the left side of the colon should be treated by a proximal colostomy and if possible resection of the site of bleeding or perforation. The distal colon may be managed by a mucous fistula or Hartmann's procedure.[22,24,90]

Patients with regional enteritis or chronic ulcerative colitis may also develop perforation while being treated with various forms of steroid therapy. In these situations it is unlikely that the perforation is the result of steroid therapy but rather the underlying disease of the bowel. If perforation is present, both the complication and the underlying disease should be treated by the appropriate surgical procedure. In the case of ulcerative colitis this implies either total coloproctectomy or a subtotal colectomy with an ileostomy. If the primary pathology involves inflammatory disease of the small intestine, then resection and a primary anastomosis may be necessary.

Massive bleeding from colonic ulceration has been reported to occur in patients while receiving prednisone therapy.[129] Although this complication may present in a setting of diverticulosis, it also has been reported in recipients of renal allografts[129] and from ulceration of the cecum.[141] The relationship of this type of ulceration to cytomegalovirus infection has been noted and may be related to the prolonged administration of steroid therapy.[2,56,80] An alternative approach to surgical intervention for intestinal bleeding involves selective mesenteric arterial catheterization with direct infusion

of vasoconstricting agents into the appropriate artery. This technique, useful in controlling bleeding in the extremely poor risk patient, will in some instances accomplish permanent cessation of bleeding.

Pancreas

The observation that acute pancreatitis can be induced in cortisone-treated rabbits[128] stimulated Carone and Liebow[25] to review pancreatic tissue obtained at autopsy from patients who had been treated with corticosteroids. They noted post mortem evidence of acute pancreatitis and or peripancreatic fat necrosis in 28% of patients receiving cortisone as opposed to 3.7% of those not receiving steroid therapy. Although hyperlipemia was known to occur with glucocorticoid treatment, these investigators were unable to implicate pancreatic fat embolization as a causative factor. One etiologic possibility may relate to the involvement of the pancreas with cytomegalovirus as noted by Tilney[134] in patients receiving steroids after renal transplantation. This association with a viral infection may explain the low incidence of this disease process when considering the large number of patients receiving corticosteroid therapy. Recognition of acute pancreatitis during corticosteroid treatment has been reported by others and found to have a high mortality rate.[7,14,98,109,118]

Patients developing acute pancreatitis during treatment with steroids have a variety of symptoms ranging from mild abdominal pain and minimal physical findings to those of acute severe abdominal pain with peripheral vascular collapse. The seriousness of the illness may parallel the amount of pancreatic tissue destruction. Acute hemorrhagic pancreatitis particularly after renal transplantation[134] is an especially fulminating disease. Other patients develop intermittent abdominal pain, distension and tenderness which persist for several weeks before gradual improvement occurs.

The diagnosis of acute pancreatitis must be considered in all patients developing sudden abdominal pain while receiving steroid therapy and may be difficult to differentiate from gastroduodenal ulceration.[118] The clinical symptoms include abdominal pain, nausea and vomiting associated with fever, epigastric tenderness and abdominal distension. Leukocytosis and elevated serum amylase are often noted as are the usual radiologic findings.

Mortality is considerable even when the diagnosis is correctly established,[109] and proper patient management should be initiated at the earliest moment. Treatment, largely supportive and similar to that used in patients with acute pancreatitis of other causes, includes nasogastric suction, antibiotics, analgesics and intravenous fluids. The withdrawal of corticosteroid therapy has been proposed, but there is little evidence that this will diminish the severity of the attack or shorten the duration of the illness. In many instances steroid therapy is of long duration thus making it impossible to achieve a rapid reduction in dosage. Surgical intervention in the past has been avoided whenever possible unless coexistent intra-abdominal conditions require exploratory laparotomy.

Wound Healing

The impairment of wound healing during adrenal steroid therapy was recognized first in 1949 in patients with soft tissue injury who exhibited minimal formation of granulation tissue while receiving ACTH.[106] These observations were confirmed and extended in the experimental animal using the rat or rabbit model.[1,38,86,101,107,115] In general it may be stated that cortisone administered before or at the time of surgery impairs wound healing as determined by tensile strength and histologic evaluation of the tissues. If cortisone is given several days after surgery, the same degree of impaired wound healing does not occur. However, it should be noted that an accurate comparison of the various published experiments is difficult because of different species of animals using varying types of dosage schedules, duration of treatment and methods of evaluating wound strength.[100] Recently anabolic steroids have been noted to increase the rate of wound healing and when given in conjunction with corticosteroids, have restored the rate of incisional healing to normal.[38]

The translation of impaired wound healing from experimental observations in animals to the clinical setting is difficult since few clinical studies are available. Green[58] compared incisional wound healing in 38 patients receiving steroids requiring colectomy or splenectomy with 22 patients not receiving corticosteroids and undergoing the same operative procedure. Wound complications were noted to be five times more common in those patients receiving steroids. The length of time steroids were given preoperatively did not seem to be a significant factor in the incidence of postoperative wound complications. More recently Enquist[39] compared the incidence of postoperative wound complications in patients receiving corticosteroids and noted the incidence in this group to be 44% as compared to 22% in the control group. Wound infection in patients undergoing renal transplantation and also receiving azathioprine varies with the institution but has been reported to be less than 2%. However, if the incision has to be reopened, the incidence of wound infection increases to 18%.[119]

From the data available it appears that steroids

given before or at the time of operation in animals impairs wound healing and in the clinical setting under similar conditions is associated with a higher incidence of infection and disruption of the operative incision.

Skeletal System

Avascular necrosis of bone has been associated with a number of diseases including rheumatoid arthritis, Gaucher's disease, caisson disease, systemic lupus erythematosus, some of the hemoglobinopathies and chronic alcoholism.[68] More recently the association of this pathologic process has been related to the exogenous administration of glucocorticoid therapy as well as the increased endogenous steroid levels found in Cushing's disease.[26,47,82] The association of exogenous steroid administration and avascular necrosis, suggested for the first time in 1957,[104] was followed by other reports in 1960[67,130] and 1963.[13] Avascular necrosis in the renal transplant patient recognized by Starzl *etal.*[125] in 1964 has been reported thereafter by a number of observers[17,32,63,64,66,72,103] and occurs in 5 to 18% of patients maintained on steroids for more than one year.

The relationship of steroid therapy to the pathogenesis of avascular necrosis was suggested experimentally when rabbits treated with corticosteroids were shown to develop histological evidence of focal necrosis of bone.[33,49,70] The presence of radiologic osteoporosis was also associated with a marked rise in serum lipid levels and fatty deposition in the liver with focal necrosis.[48,49] These experimental observations were supported by the earlier clinical observation of avascular femoral head necrosis reported in a renal transplant recipient dying from systemic fat embolization.[72] Fat globules demonstrated in the subchrondral channels of the affected femoral head of this patient at autopsy were later demonstrated in rabbits treated with intramuscular cortisone.[70] Others,[41,64] however, have not noted the same histopathologic findings of fat embolism, and therefore, the etiology and pathophysiology of avascular necrosis with steroid therapy remain open to question. There is no apparent relationship to age, sex or primary renal disease in the renal transplant population.

Several attempts have been made to correlate the disease with the dosage of cortisone and prednisone. Although some have suggested a dose relationship,[66] others have concluded that there was no evidence for this as an etiologic factor.[103] Furthermore, some patients develop the disease on relatively low dose therapy whereas others tolerate prolonged high dose steroid therapy without difficulty. Although corticosteroids participate in formation of avascular necrosis, the combination of hemodialysis, renal osteodystrophy and hyperparathyroidism may also be contributing factors.

The joint most commonly involved is the hip, followed by the knee, ankle, shoulder, elbow and wrist. The disease process usually occurs within three to 24 months after onset of steroid therapy. The earliest symptoms are those of pain aggravated by exercise and at first relieved by decreasing physical activity. As the disease progresses, pain becomes constant, progressively more severe and unrelated to physical activity. Pain due to aseptic necrosis of the hip is often referred to the knee, whereas the same process in the knee, ankle and elbow may present with pain and on occasion joint effusion.

Early diagnosis depends upon the radiologic appearance of the bones in question demonstrating subchondral resorption of bone in the femoral head, humeral head, distal femur or proximal tibia.[32] These lesions enlarge and ultimately develop cortical collapse. Impaired range of motion is minimal early in the disease and increases as skeletal and cortical collapse continues. Serum calcium and alkaline phosphatase levels are seldom abnormal in these patients.

The nonoperative treatment of advanced avascular necrosis is generally unsatisfactory, and since the etiology is unknown, there are no measures available for prevention or retardation once the disease process begins. Partial weightbearing provides symptomatic relief; however, there is little evidence that progressive collapse of bone matrix is altered. When pain or limitation of motion is severe, joint replacement has been effective in restoring function and alleviating pain. Reduction of the steroid dosage has been recommended; however, once the pathologic process starts, there is no evidence to suggest that this will retard or stop the disease process. Some[66] have suggested that aseptic necrosis can be minimized in the post transplant patient if the total steroid dose is reduced. Alternate day steroid therapy may be associated with a lower incidence of aseptic necrosis than that reported with daily administration and may be advantageous in diminishing the incidence of the disease process.[120]

The surgical approach to avascular necrosis of the hip and other weightbearing joints has been increasingly directed toward joint replacement.[41,47,66,94] The results of femoral head prosthesis have been especially satisfying in relieving pain and improving ambulation.[47]

Anesthesia

Surgical intervention in the patient with Addison's disease prior to corticosteroid replacement therapy was associated with a high mortality (78%) during the first two postoperative weeks, largely the result of

adrenal insufficiency.[59] The subsequent development and clinical use of adrenal steroid preparations have enabled the patient with Addison's disease to withstand the stress of both anesthesia and the operative procedure. In 1953 adrenal insufficiency was recognized to occur post-operatively after prolonged administration of cortisone with the suggestion that larger dosages of corticosteroids might be necessary during the operative and postoperative period.[51] Similar reports followed,[8] and various pharmacologic protocols were developed for the management of patients receiving adrenal steroids before, during and after surgical intervention.[99,117,123] It is of clinical significance that the natural history of pituitary-adrenal recovery after prolonged suppression with corticosteroids requires at least 9 months before plasma ACTH and 17 hydroxycorticosteroid levels returned to normal[57] (See Fig. 1). Graber and associates[57] noted that immediately following the cessation of exogenous steroids, only minimal ACTH is secreted in spite of low levels of plasma 17 hydroxycorticosteroids. When the pituitary gland does begin to secrete ACTH, the adrenal glands continue to lag behind for several months before complete recovery. Six to 9 months after termination of exogenous steroids both plasma and urinary 17 hydroxycorticosteroid levels return to normal even though adrenal gland responsiveness may still require above normal ACTH stimulation to maintain normal plasma 17 hydroxycorticosteroid levels. After 9 months patients were found to have normal levels of plasma ACTH, plasma and urinary 17 hydroxycorticosteroids and a normal adrenal response to ACTH. Thus, with profound suppression of ACTH for a long period of time the pituitary gland secretes little ACTH even though corticosteroid levels are deficient. When the pituitary gland does resume secretion of large quantities of ACTH, the adrenal glands may still not recover their normal degree of responsiveness for several more months.

The preoperative, intraoperative and postoperative management of patients receiving corticosteroids has been reviewed in detail.[23,57,99,131,132,137] Regardless of the exact dosage of steroids used, it is preferable to prepare patients the evening before surgery with glucocorticoids as well as immediately preoperatively, intraoperatively and postoperatively. Patients receiving steroids 4 days or longer within 6 months of surgery should receive prophylactic treatment in the pre and postoperative periods.[57,137]

One such treatment schedule includes the administration of 100 mg hydrocortisone i.m. the evening before surgery, 100 mg i.v. immediately prior to surgery, 100 mg i.v. during surgery and 100 mg i.v. the evening of the day of surgery. The amount of steroids given postoperatively can be rapidly tapered from 300 mg per day of hydrocortisone on the first day to 200 mg on the second day and 100 mg on the third day. Subsequent reduction will depend upon the preoperative dosage. If the patient has been maintained on a substantial dosage (i.e. prednisone 10–40 mg/day) before surgery, then the only additional steroid coverage necessary will be during the day of surgery. Postoperatively the maintenance steroid dosage may be resumed.

Infection

The relationship between administration of adrenal corticosteroids and infection has been recognized for more than 20 years.[74,76,111,133,135] Kass and Finland[74] in 1953 clearly outlined the pathologic effects of cortisone and ACTH upon the resistance of laboratory animals to a wide variety of bacterial, viral, protozoal and fungal organisms. They noted that cortisone and ACTH may: 1) activate latent infections rendering animals susceptable to non-pathogenic organisms of the respiratory or intestinal tract; 2) diminish host resistance; 3) decrease the local inflammatory response and be associated with widespread dissemination of infection; and 4) cause infected animals to die from lesser numbers of microorganisms than normally. These experimental observations have been supported by a retrospective review of patients dying with Cushing's Syndrome.[105] Subsequently, it was confirmed that patients treated with steroids are clearly at an increased risk from a variety of opportunistic infections.[4,52,110,121,135]

The incidence of wound infection in transplant patients undergoing operation while receiving adrenal corticosteroid therapy has been reported to vary from 1.8% to 56%.[19,93,119] It is difficult to separate the contributing role of steroids in these patients since most have a recent history of uremia, some are insulin-requiring diabetics and all receive additional immunosuppressive therapy such as azathioprine or cyclophosphamide and in some instances antilymphocyte serum. Although statistical data are not available, it would appear that most wound infections in transplant recipients are associated with wound hematoma or urinary fistulae requiring re-exploration and are not the result of corticosteroids.[78,79]

Corticosteroids administered in large dosages cause both a neutrophil and lymphoid response as well as changes in the reticuloendothelial system.[9] Although poorly understood, the inflammatory response is impaired particularly during the early phase of vasodilation and the adherence of leukocytes to the endothelium. The mechanism of the anti-inflammatory

effects of steroids has been considered to be secondary to an interaction between histamine and complement, but the exact explanation remains unknown. It is apparent, however, that the effects of glucocorticoids upon the inflammatory response[12] and cellular immunity[15,50] are critical in changing the normal pattern of host response and collectively responsible in various ways for the increased susceptibility to infection. Of interest is the more recent observation that the half life of neutrophils was prolonged in patients receiving alternate day prednisone as opposed to daily steroid therapy,[35] and was also related to the steroid dosage. Alternate day prednisone therapy appears also to cause a redistribution of circulating lymphocytes to other body compartments[42] thus producing a cyclic and transient monocytopenia and selective lymphocytopenia.[43] These observations may provide at least a partial explanation for the reported decreased susceptibility of infection in those patients receiving alternate day prednisone as compared to those treated with daily steroids.

The clinical sequelae of long-term glucocorticoid therapy in terms of impaired host defense mechanisms can be best surveyed in immunosuppressed recipients of renal allografts and in patients with malignant neoplasms treated by chemotherapy. Particular risk factors in these transplant patients include hyperglycemia, renal failure and leukopenia.[4] Gram negative bacterial pulmonary infections have been recognized to be serious and often fatal complications in renal transplant patients.[18,95] Fungal infections including candidiasis,[52,110] nocardia,[6,52] aspergillosis,[21,52] cryptococcosis[52,110] and histoplasmosis[110] have been reported in renal transplant patients receiving prednisone in combination with azathioprine and on occasion antilymphocyte globulin. *Pneumocystis carinii*, noted to occur in a variety of clinical situations including patients with congenital and acquired immunodeficiency disease, is a serious and often fatal complication in patients receiving adrenal corticosteroids.[20,139] Viral infections in the same group of patients have been noted with increasing frequency and include cytomegalovirus and Herpes simplex virus.[45,91,110,121] Both may be reactivated from a latent infection and involve a number of organs including the brain, gastrointestinal tract, liver, pancreas, lung and kidney. In some instances cytomegalovirus, as mentioned earlier, has been noted to occur in mucosal ulcerations of the stomach, small and large intestine, raising the question of their etiologic role in this disease process.[2,89,113] Herpes simplex, considered in most instances to result from activation of endogenous varicella-zoster virus from a latent state, has also been reported in patients receiving immunosuppressive therapy.[2,91,110] Disseminated toxoplasmosis has been reported in patients receiving corticosteroid therapy for malignancy and as immunosuppressive therapy after renal transplantation.[27] The ability of cortisone to impair cellular immunity by reversing positive skin tuberculin tests to negative[15] suggests that the incidence of tuberculosis in patients receiving corticosteroid therapy might also be increased. Surprisingly, tuberculosis has not been reported to be a frequent infection in patients receiving corticosteroid therapy[96,110] and seems to be less common than other opportunistic diseases.

Cataract Formation

Posterior subcapsular cataract formation, first reported to be a complication of long-term systemic steroid therapy for rheumatoid arthritis,[11,36] has more recently been associated with the use of corticosteroids as immunosuppressive therapy after renal transplantation.[10,46] Although cataract formation has been known to occur with as little as 5 mg/day of prednisone within a two month period of treatment, the incidence appears to be related to both dosage and duration of treatment.[10,11,46] Children appear to be especially at risk,[46] but this observation may merely reflect the high steroid dosage on a mg/kg basis used in the early post transplant period. Cataract formation may be unilateral or bilateral, and there appears to be no sex predisposition. The pathogenesis of posterior subcapsular cataracts is obscure and does not seem to relate to the underlying disease, serum calcium or cholesterol, renal function and the other side effects of corticosteroid therapy. Intraocular pressure is rarely increased. Treatment is symptomatic, but if the decrease in visual acuity is severe, cataract extraction may be necessary. Whether or not alternate day therapy will lessen this complication as suggested[120] remains to be determined by further clinical studies.

Pseudotumor Cerebri

The syndrome of pseudotumor cerebri reported to occur with a number of conditions has also been related to the use of corticosteroid therapy in children.[60,138] The duration of adrenal steroid treatment may extend from months to years, and the stigmata of Cushing's Syndrome are usually present. The symptoms often occur shortly after a change in steroid dosage and include headache, nausea, vomiting, diplopia, drowsiness and stupor. Bilateral papilledema is usually present with an abnormal electroencephalogram. Pneumoencephalography may reveal an abnormal position of the ventricles with usually normal spinal fluid pressure and protein.

The pathogenesis of the condition is unknown but has been related to brain edema resulting from corticosteroid therapy. Treatment has been the empirical increase of the daily steroid dosage followed by gradual reduction. The signs and symptoms of this syndrome have been observed to subside after a period of weeks to months.

Conclusions

For the past 25 years the clinical use of adrenal glucocorticoids has become a valuable means of symptomatic relief for many diseases, a necessary form of treatment on a short and long-term basis for many of the collagen and hypersensitivity diseases, and essential for permanent therapy in patients with adrenal insufficiency and recipients of organ transplants. The serious and occasionally fatal side effects secondary to the prolonged use of corticosteroids are significant and may occur in an acute or chronic situation. The surgical management of these complications is often associated with a high morbidity and mortality as a result of both the patient's underlying illness and the complication itself. A better understanding of the pharmacologic effects of steroid therapy upon the primary disease will allow a more accurate determination of dosage thereby eliminating some of the undesired side effects related to excess administration of the drug. The development of new anti-inflammatory drugs may eventually replace the use of steroids and thereby eliminate the associated morbidity and mortality. In those instances where long-term adrenal corticoid therapy is essential, the alternate day dosage schedule may decrease the occurence of the infectious complications resulting from excessive immunosuppression.

Until the above mentioned alternative solutions become available only a thorough understanding of the pharmacology and physiology of adrenal corticosteroids and their potential side effects will enable the physician and surgeon to either prevent or recognize and treat the serious and often life threatening complication of these drugs.

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